Aus der Universitäts-Kinderklinik Bern (Jennerspital)
Direktor: Prof. Dr. E. Glanzmann

TYPHOID AND PARATYPHOID IN CHILDREN

A Clinical Study

INAUGURAL-DISSERTATION

zur

Erlangung der Würde eines Doctor medicinae
der Universität Bern

vorgelegt von

Martin Dinep

von New York, U.S.A.

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INTRODUCTION

In this paper we propose to present first a short review of the classical picture of typhoid and paratyphoid fevers as found in the literature. There follows then a review of the clinical picture as found in the cases of typhoid and paratyphoid fever which have been admitted to the Jenner-Spital since the initiation of chloramycetin therapy. Special note is made of one case of parotitis typhosa.

HISTORY

Although the exact delineation of typhoid fever and typhoid-related or simulating diseases is relatively modern, we find described in the writing of Hippocrates diseases that might well fit into one of these categories. (24)

Closer to modern times, Spiegelius (1624), in a study of the diseases to be found in Padua, discusses an illness that encompasses "typhoid" symptoms and an inflamation of the ileo-coecal region. Willian, in 1659, and Baglini, in 1696, described diseases with a similar clinical picture.

In 1737 Huxham recorded an epidemic of "nervosa lenta" which, point for point, matches the clinical picture of what we now call typhoid fever.

In the 18th century an attempt was finally made to differentiate the individual diseases that had been included under the general heading of "Typhoses". Efforts were then directed toward dividing them according to contagiousness, pathogenesis, and form of crisis. Later, a division was made into putrid and malignant forms.

It was known, however, that the disease occurred through contact with a diseased patient or with dirty rooms, hospitals, and prisons.

During this period, examination of the patient was limited to the pulse, tongue, urine, and stool, but several authors did make note of the characteristic roseola typhosa.

The first exact pathological-anatomical studies were undertaken by Peyer and Brunner in 1677 and intestinal ulcerations were described. In 1762 the work was carried further by Morgagni, who studied not only the large intestine, but the mesenterial glands, the spleen, and the lungs as well.

It was not until the 19th century, however, that a coordinated picture of a disease entity began to emerge. For this we must thank a large number of workers in various parts of Europe.

The strife existing between protagonists of the various theories concerning the etiology of typhoid fever was ended by Eberth's identification of the typhoid bacillus in the mesenterial glands. These findings were confirmed by Koch, and in 1890 the bacillus was morphologically and culturally separated, in the pure form, from other intestinal forms.

In 1896 Gruber, Durham, and Widal developed the agglutination. Paratyphoid bacilli were separated in 1897 on the basis of negative seroagglutinations.

This work was carried further in 1900 by Schottmuller, and resulted in etiological differentiation between typhoid and paratyphoid, as well as the further delineation of paratyphoid A and B. In the next year, positive blood cultures were produced. (5)

Since that time, the further study of pathogenesis and the search for a cure have been the chief concern of researchers.

PATHOGENESIS

When typhoid bacilli are ingested, they and the body may react in several ways. They may cause a local gastroenteritis with a more or less acute course and nothing else, or they may cause no immediate intestinal symptoms, but, instead, penetrate to the lymph vessels and be carried to the mesenterial lymph glands. This is the location in which the disease develops.

This ability of the typhoid bacillus to cross the normal intestinal lymph barrier is a basic difference between it and nonpathogenic intestinal bacteria. It is a question here of a spreading factor, such as one finds in haemolytic streptococci, staphylococci, pneumococci, etc. Just as metabolic products of the body may be freely transportable, so may pathogenic bacteria cross the functional unit of protective substrata. It is possible to conceive that under the influence of a spreading factor the wall of blood vessels may be made permeable to a plasma-insoluable substance. Also, through the working of a spreading factor, bacteria can follow this path as long as no counter-ferment, anti-hyaluronidase increases the viscosity of the connective tissue. (2)

Typhoid bacilli can be transported from the mesenterial glands as follows:

a. Retrograde to the lymph vessels of the skin. This leads to the development of roseolae, which are often much more numerous in paratyphoid than in typhoid and are, in the former, less likely to be limited to the abdomen. (20) In typhus the reaction takes place in the blood capillaries, but it may be quite difficult to differentiate between the two locations.

b. Typhoid bacilli are transported back to the lymphatic structures of the intestines, particularly the lower ileum and coecum, as high as the transversum, and produce

in this region an inflamitory reaction: swelling, necrosis, ulcers with and without bleeding, and possibly perforations and peritonitis.

c. The third main route is over the ductus thoracicus into the general circulation, and by means of this bacteriaemie the various organs may be infected. There is, however, no growth of the bacteria in the blood.

From the above-noted spread we must conclude at present that typhoid and paratyphoid, in their generalized stages, consist of a lymphatic sepsis and a bacteriaemic component, with the mesenterial lymph glands acting, for a limited time, as a constant source of bacteria. Theoretically, there is no limit to the possible metastasis.

There are a number of theories as to the true cause of illness. The old enterogen theory was revived by Graeff (8) in 1917. According to this theory, typhoid fever is a specific reaction of the organism which is activated by the specific exciting agent. The form is determined by the specific tissue changes, in the center of which is the typhoid tubercle, caused by the causal-defense counter-working.

These tubercles, lymphom or typhom, result from the action of the typhoid bacilli and their toxins, and consist of focal proliferations of macrophages. (1)

CLINICAL PICTURE

The pathogenesis of typhoid and paratyphoid is fundamentally the same. The difference between the two lies in the clinical picture.

In Typhoid, during the last few days before the appearance of the fever, the patient often complains of headache, dullness, pains in the limbs, and a reluctance to work. Sleep and appetite are disturbed.

Occasionally, laryngitis and a light bronchitis, with a sub-febrile temperature which climbs stepwise, heralds in the disease. Angina with sore throat, accompanied by swelling and inflamation of the pharynx mucosa, was observed by Jochman (11) in one case. This occurred with a one-day fever, immediately before the true appearance of the fever phase of the disease.

A rapid temperature climb with acute chills is very seldom. One is more likely to observe this in paratyphoid than in typhoid.

The fever usually reaches a level of 40-41° C after five to ten days of climbing stepwise, and maintains a continua with slight daily remissions for one or two weeks or longer, then slowly drops by lysis or with deep morning remissions, while the evening temperature drops stepwise. In some cases the lysis may proceed to sub-normal levels. (4)

Jochman (11) divides the fever periods as follows:

a. Stadium incrementi: first week; swelling of the solitary follicles and Peyer's patches.
b. Stadium acrmes: second-third weeks; necroses and ulcer bilding.
c. Stadium decrementi: fourth week; healing.

In the first week the skin is dry and warm. The tongue is coated and dry, the edges and tip inflamed. The tonsils are often swollen and inflamed. There is a tendency to nosebleeds. In rare cases the ileocoecal region is tender upon pressure. Sometimes the patient complains of abdominal pains. The stools are still more or less normally formed during the first week.

The spleen is usually enlarged within the first few days of the disease and is palpable. Hartwig (9) states that in children this increase is often demonstrated only through fullness in the Traube's space.

In the second stage the temperature maintains itself in the neighborhood of 40° C. The sensorium is greatly disturbed, producing the typical "Status Typhosus", the clouding of consciousness. During the day the patient is apathetic to a point where he must even be fed. He answers in single syllables and sleeps or dreams throughout the day. The face is usually red and often slightly cyanotic, but not swollen as in typhus. The typhoid patient often presents a typical odor.

At night the patient is usually restless, often slightly delirious. In severe cases any degree of disturbance, to the depth of full coma, is possible.

The abdomen is distended and marked meteorismus is frequently evident.

Diarrhea three or four times a day with the classical pea soup stools may be present, or constipation may exist throughout the course of the disease.

The spleen develops to a large soft tumor, although the increase in size is often difficult to determine because of the meteorismus.

Roseolae are small, round, slightly raised, pale red eruptions varying in size up to that of a lentil. They are usually present in small numbers, five to twenty, and appear on the skin of the abdomen and lower chest. They blanch when pressed with a finger or spatula. The individual roseolae lose their color after four or five days, but new ones appear throughout the duration of the fever. Only in rare instances do they extend to other parts of the body.

The tongue is dry and, by poor nursing, fuliginous and crusted.

The bronchitis is increased with rhonchus and rales, particularly over the lower lobes.

The pulse is usually dicrotic and continues relatively slow, but the vagus-determined bradycardy is often lacking in children and older people. (9) In cases of severe

bacteremia, there may be a weakening of the heart due to the infection. This causes a small, rapid pulse and a disappearance of the dicrotism. The extremities become cool and cyanotic, and, with a continually falling blood pressure, death may ensue.

The third week is primarily the period of complications: pneumonia, intestinal perforation, peritonitis, nephritis, laryngitis, and decubitus are just some of the possibilities.

At the end of the third or fourth week the fever falls. The sensorium clears and sleep is more peaceful. The patient is easily tired, however, and sleeps much of the time. The roseolae fade and are not replaced. The tongue regains its normal condition. The spleen decreases in size and a general return to normal is observed. There is an increase in the amount of urine, which is pale. In cases with deep morning remissions, there is often now an acute outbreak of perspiration. Small, water-clear blisters appear on the chest and abdomen.

During the convalescence one becomes aware of the extensive wasting. The patient is anaemic, a large part of the fat reserves have been utilized, and the muscles are flacid. The skin peels in clover-shaped flakes and there is a temporary loss of hair.

The fever picture must be carefully watched, as an abnormal curve, particularly in the third week, may be the first indication of complications. Sudden climbs of temperature are often accompanied by chills, which are otherwise very rare in typhoid fever. Chills are sometimes also encountered as the temperature begins to climb again, following a marked drop in temperature brought about by medication.

A sudden drop in temperature occurs also in cases of intensive intestinal bleeding. This is more or less pathogenomic for collapse. (11)

In severe cases the lips exhibit small tears and are covered with black crusts. Moderately severe cases often display a dark, wine-red color which is in sharp contrast to the pale face. (11)

The gums bleed easily, cheilosis is present, and ulcerations may be found on both the hard and soft palates. Swelling and inflamation of the tonsils are often prodromal signs. Some authors speak of a tonsillo or pharyngo-typhoid (11, 23) in which difficulty in swallowing is present from the beginning, and white, slightly raised spots are observed. These later produce ulcers. It is possible from this locale for the infection to involve the neighboring areas. It is difficult to say in specific cases whether the parotitis that may be observed during the third week or during convalescence results from metastasis or from direct extension from the mouth.

A secondary infection may complicate the primary picture, with abscess building or penetration outward or into neighboring structures. A sinking, into the region of the vena jugularis, can easily cause thrombophlebitis and sepsis.

In general, Paratyphoid B follows a course similar to that of a mild or moderately severe case of typhoid. Glanzmann, [6] however, sets forth a number of differences which should facilitate clinical differentiation.

The incubation time for paratyphoid is usually shorter, approximately five days. The onset is more sudden, and, in most cases, is accompanied by vomitting, chills, and a rapid climb in temperature. Fever cramps are frequently observed in children.

The stools may contain considerable mucous and resemble those of dysentery.

The temperature curve resembles that of typhoid, but with a more rapid climb and, often, a sudden drop. A temperature curve of shorter duration and greater irregularity is also characteristic.

Roseolae may appear at the end of the first week, and are frequently exceptionally profuse and small, or scanty and large.

The neurological symptoms are milder than those of typhoid. The blood and urine pictures are the same. The prognosis is good.

Glanzmann cites four clinical types of paratyphoid:

1. Typhoid form: The classical type, with neurological symptoms, enlarged spleen, roseolae, diarrhea, etc.
2. Gastro-enteritic form: A gastro enteritis, with fever and roseolae.
3. Dysenteric form: Consisting primarily of a colitis.
4. Paratyphoid sepsis: Sepsis of the newborn, due to a diaplacental infection.

Strong [20] goes even further and describes, in addition, a nephritic type, a rheumatic type, etc., which he says are based on the fact that paratyphoid bacteria have less tendency to remain localized than do those of typhoid.

In view of Strong's statement, it is surprising that more cases of parotitis-typhosa due to paratyphoid B have not been reported in the literature. Our cases of typhoid and paratyphoid fevers fit into this classical schema, although, of course, none of them present all the classical symptoms.

CLINICAL OBSERVATIONS

Particular cases observed at Jenner Children's Hospital, Bern, since the introduction of chloromycetin into the treatment of enteric fevers, with special note of one case of parotitis typhosa:

12 cases of paratyphoid B (1 complicated by parotitis)
3 cases of typhoid fever

The patients ranged in age from 1.5 years to 12.0 years, the average being 5.3 years.

The patients had been ill a minimum of four days and a maximum of thirty-five days upon admission, the average being twenty days.

In all cases the patient presented a strong pulse upon admission and maintained such throughout the course of the disease. In no case was a pulse under 100 per minute observed; however, a rate of 160 was observed in one case.

The temperature variations were not extensive. Morning temperatures were 38° C, plus or minus one degree; evening temperatures were 39° C, plus or minus one degree.

The temperatures fell within 1 to 15 days after beginning treatment with chloromycetin, the average time being 6.1 days. *)

Clinical Observations (cont'd)

	Number of Cases	%
Enlarged lymph glands	7	46.7
Tongue coated	7	46.7
Headache	3	20.0
Prodromal temperature	13	86.7
Constipation	3	20.0
Roseolae	10	66.7
Gross intestinal hemorrhage	3	20.0
Halinated eyes	5	33.3
Enlarged spleen	5	33.3
Enlarged liver	5	33.3
Malaise	13	86.7
Abdominal pain	7	46.7
Diarrhea	6	40.3
Vomitting	5	33.3
Neurological signs	1	6.7
Enlarged and inflamed tonsils	8	53.3
Parotitis	1	6.7
Cough	1	6.7
Respiratory difficulties	2	13.4
Exanthem	2	13.4
Epistaxis	1	6.7
Positive blood clutures	1	6.7
Positive stool	10	66.7
Positive agglutination	15	100.

*) One patient was discharged without signs of improvement after 7 days, because the parents were leaving the country.

In two cases, both from the same family, there developed during the course of the disease an exanthem, which closely resembled that of measles. In one case this was combined with conjunctivitis, bronchitis, and a fine, grey-white outbreak over the mucous membrane of the mouth. In the other case the cervical submandibular and axillar glands were enlarged. The pulse was 100, the tongue brown and thickly coated, and the mouth coated with minute specks. The tonsils and throat were inflamed. Two days later epistaxis occurred.

The exanthem lasted seven days in the first case and four days in the second. The exanthem traces that remained were red, rather than the brown of measles. (6) There was a relative lymphocytosis and leukopenia. The throat cultures were negative for diphtheria and hemolytic streptococci.

The exanthem was attributed to the presence of paratyphoid B in both cases.

The one case of paratyphoid parotitis presented the following history:

Previous illnesses: Tonsillectomy at the age of five; otherwise, nothing pertinent.

History of present illness: Five weeks previous to admission there was a glandular swelling in the region of the neck. Pain. Temperature of 38,5° C. Condition persisted for one week.

Two weeks previous to admission: Ear and throat pain. Temperature 38° C, higher in the evening than in the morning. This lasted for four days.

Four days previous to admission: Temperature was 39° C. The neck glands were swollen once again.

Day previous to admission: The patient received penicillin.

On admission: The temperature is 40° C. The ears and throat are practically normal. There is no longer any pain. There was an eight-day period without any stool and then one spontaneous passage followed by a further three-day period without passage, which brings us up to the present day. The patient has lightly halonated eyes and impresses the observer as being tired and ill. There are several pinzead-sized efflorescences. They are slightly raised and blanch on pressure. They are located primarily on the chest with somewhat smaller ones on the back.

Lymphglands: The submandibular glands are almond-sized, indolent, and soft. Except for these, the head and neck glands are free. The axillar region presents several pea-sized, soft, indolent, freely-movable glands The inguinal glands are palpable but small.

The liver is palpable two fingers below the ribs in the midclavicular line, soft, indolent.

The spleen is just palpable.

There is a light rhinitis.

The tongue is somewhat dry and slightly coated white. The throat is not inflamed.

The patient was started on:

Chloromycetin 4 x 250 mg
Redoxon 500 mg
Becocym 2 x 1 tabl. forte

Third day after admission: The report was received that the agglutination for paratyphoid B Schotmuller was positive 0 1:100, H 1:400. The patient passed a stool today.

Fourth day: The temperature has fallen to normal. There are two small roseolae on the chest. The patient complains of pain on the left side of her neck. There is, however, nothing to see. An antiphlogistine binding was applied. Two hours later a clearly perceptable swelling of the left parotis was observed. The papilla was inflamed. The temperature climbed to 38.2° C. The patient is Moro positive (TBC innoculated), Pirquet negative.

Fifth day: The area of the left parotis was smeared with Salenal sulfe.

Sixth day: There is a decrease in the swelling of the left parotis. There is, however, an extremely painful, hard, nut-sized, right submandibular gland.

Seventh day: The left parotitis is greatly improved, only slightly swollen, and the duct is no longer inflamed. On the right, there is a diffuse swelling extending from the submandibular gland. Temperature 37.6° C. The patient's general condition is better. Her appetite has improved. She is more alert and reads a little. Roseolae are now absent. The tongue is still coated, however, and the stools fairly fluid.

Eleventh day: There are no longer any signs of parotitis. The right submandibular gland is also normal in size, but still hard. The child is afebril. The tongue is still coated, but the stools are now normal. Appetite good.

Nineteenth day: The right mandibular gland is slightly swollen again. The patient appears ill. Salenal dressings were again applied. The stool is negative for salmonella.

Twenty-first day: Stool negative, chloromycetin decreased.

Twenty-seventh day: Chloromycetin stopped.

Thirtieth and thirty-third day: Stools negative.

Forty-fourth day: The patient was discharged.

Summary of case:

The patient was admitted after a five week history which was dominated by recurrent fever, pain, and glandular swelling in the neck, as well as enteric disturbance and typical roseolae. It was only on the fourth day after admission, however, that the recurrence of neck pains was followed by a swelling of the left parotis and inflamation of Stenson's duct. This was accompanied by a rise in temperature to 38.2° C, after this had previously fallen to normal under chloromycetin therapy. After three days of local therapy with salenal sulfe, there was marked improvement in the patient's general condition and reduction in the swelling of the parotis. There was, however, swelling in the area of the right submandibular gland.

Seven days after its appearance, there were no longer any signs of parotitis and the right submandibular gland was, although still hard, normal in size. The child was afebril. On the fifteenth day after the appearance of the parotitis (that is, the nineteenth day after admission), there was again a slight swelling of the right mandibular gland and a decline in the patient's condition. This responded rapidly, however, to the local application of salenal dressings.

During all of this period, chloromycetin therapy had been continued. On the twenty-first day after admission, the stool was reported negative, as were the two successive stools. On the twenty-seventh day, chloromycetin therapy was discontinued and the patient's recovery continued without incidence.

SUMMARY

Our figures are too limited to allow any sweeping conclusions, but if we try to relate them to other statistical studies we do find some interesting comparisons. Stuart, (21) in his study of 360 cases of typhoid infections, reported constipation in 78 % of his cases, as compared to 20 % in our cases. Hartwig (9) also reports 66 % of his patients constipated. As to gross intestinal hemorrhage, however, Stuart reported 21 %, as compared with our figure of 20 %, and this despite the fact that our patients received chloromycetin which was not available at the time of Stuart's study. He reports enlarged spleen in 64 % of his cases. Hartwig gives a figure of 68 %. Our figure is 33 %.

Stuart reports malaise in 87 %. Our figure is also 87 %. Stuart's figure on diarrhea is 43 %. Our figure is 40 %. He found cough in 40.2 %, as opposed to 6.7 % in our cases. Epistaxis he reported in 4 %, as opposed to our 7 %. Blood cultures he reported positive in 73 % of his cases, as compared with our 6.7 %. He reported positive stools in only 26 % of his cases, as compared with 67 % in ours. His agglutinations were positive in only 65.8 %, as compared with our figure of 100 %.

Some of the discrepancies are probably a result of the fact that both the studies of Stuart and Hartwig were made during epidemics Consequently, their patients were admitted for treatment and study at an earlier stage in the disease. This would explain the low rate of positives in our blood cultures, since the average admittance of our cases was after twenty days of illness. This would also explain the discrepency in the appearance of respiratory symptoms. Of course, the average age of our patients, and the fact that every epidemic tends to display some characteristics peculiar to itself, must also be taken into account.

It is interesting, as has been noted earlier, (21) that in our cases chloromycetin did not interfer with the body's production of agglutinins. Chloromycetin also seems to be not completely successful in preventing intestinal bleeding; this fact is cited in the early works of Woodward, (22) as well as in our figures.

Because most of the cases were paratyphoid B, the relative mildness of the disease, even before the administration of chloramphenicol, is understandable.

Parotitis typhosa, as a complication of typhoid or paratyphoid, is an uncommon but important occurrence, and may present a considerable diagnostic problem, particularly during an epidemic of mumps. It occurs in less than 1 % of all cases of typhoid-paratyphoid infections. Stuart (21) reports 0.56 %. Minuto, (13) in his study of 531 cases of typhoid infections, reported 5 cases, or 0.94 %. Of these 5 cases, 4 were bilateral. Hofmann, (10) however, in his study of 19 cases, reported 15 as unilateral and only 4 as bilateral.

Since Jochman (11) first wrote of parotitis appearing as a result of typhoid, numerous cases have been reported. However, paratyphoid B as a causitive agent has proven much more rare, and, therefore, makes our case one of special interest.

The symptoms of parotitis typhosa are:

1. Swelling
2. A deficiency of parotid secretion
3. Irregular or rapidly climbing temperature
4. Pain over the mandible
5. The pre-auricular lymph glands are enlarged on the affected side, and the mucosa is inflamed and non-secreting
6. Stenson's duct is inflamed
7. Pressure on the gland results in expulsion of purulent material. (Minuto (13) cultured staphylococcus from the glandular fluid in 3 of his 5 cases. This was not observed in our case.)

In most cases spontaneous remission takes place. Within a few weeks the parotitis is no longer in evidence.

There are cases reported, (13) however, in which there is an increase in pain in the tempero-mandibular articulation and in the region of the parotis. The hard, painful knot enlarges and eventually fluctuates. Movement of the mandible is difficult, and the skin is red and painful. The result may be any of the complications which can result from an abscess of the face. Liebermeister (12) reported fatalities in half of his cases of parotitis.

Because of the seriousness of possible complications, it is essential to differentiate this condition from that of infectious parotitis. Epidemic parotitis occurs in late winter and spring, so that some overlapping of seasons can exist. The prodromal period is only one to two days with fever, anorexia, headache, vomiting, and generalized aches and pains. The temperature may rise slowly to 102-103° F. The glands on one side, or both sides, begin to enlarge. Pressure is painful and the patient often finds it difficult to open his jaws. The swelling reaches its maximum in about three days, remains at its peak for approximately two days, and then slowly recedes. The submaxillary glands on both sides are also frequently involved. The disease is bilateral in 70 - 80 % of the cases, and as much as a week or more may intervene between the swelling of the two sides.

The orifices of Stenson's or Wharton's ducts may or may not be inflamed. Unless there are complications, however, the lymph glands are not effected, and the amount of saliva is usually unchanged, as opposed to the picture in typhoid. A relative lymphocytosis exists in both cases. The picture of parotitis observed in our case, or in general, would fill this description very well. The primary difference in our case was the duration of the disease before parotitis appeared, and the pronounced abdominal involvement.

As can be readily appreciated, unless the case presents marked abdominal symptoms, or, unless purulent material is expressed from the gland, it would be quite easy to confuse the two conditions until either the basic typhoid condition manifested itself, or the purulent fluctuating gland made itself evident or broke into surrounding tissues. Fortunately, the typical picture of typhoid is usually present, and the parotitis normally appears first in the third week. (11) Laboratory studies would, of course, decide the diagnosis.

Purulent parotitis in the newborn, tumors, and other forms of secondary or infectious parotitis are not likely to present particular diagnostic difficulties.

In conclusion, I wish to thank Prof. Glanzmann for his guidance and inspiration. My appreciation also goes to the staff of the Jennerkinderspital for their kind cooperation.

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